II. REMARKS

Before the amendments made herein, claims 64 to 67, 71, 72, 76-78 and 80 to 113 were pending. Claims 64 to 67, 76 to 78, 80 to 91, 102-106, 112 and 113 have been canceled herein without prejudice. In addition, new claims 114 to 118 have been added. Accordingly, after the amendments made herein are entered, claims 71, 72, 92 to 101, 107 to 111 and 114 to 118 will be pending.

A. Regarding the amendments

Claim 97 has been amended by deleting the phrase "consisting essentially of." The claim has also been amended to recite that the claimed preparation can elicit anti-heparanase antibodies. This amendment is supported in the specification, for example, at page 65, line 13, which discloses that the preparation of the invention can do precisely that.

Claim 107 has been amended by deleting the term "recombinant." This amendment is supported in the specification, for example, beginning at page 39, line 15, which discloses the claimed polypeptide.

New claims 114 to 118 are directed to purified heparanase. These claims are supported in the specification, for example, at page 53, line 9, which discloses a preparation of purified heparanase.

Because all of the amendments made herein are fully supported by the specification, no issue of new matter arises.

B. Regarding the written description rejections

Claims 64 to 67, 72, 76 to 78, 80 to 90 and 96 to 113 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification. Applicants respectfully traverse the rejections.

1. The term "consisting essentially of"

Claims with this term have either been amended to not include the term, or such claims have been canceled herein. Accordingly, withdrawal of this rejection is respectfully requested.

2. The term "is purified close to homogeneity"

This term is fully supported by the specification and can be found, for example, at page 65, line 7, which discloses that the claimed protein "can be purified by any conventional procedure close to homogeneity." Accordingly, withdrawal of this rejection is respectfully requested.

C. Regarding the enablement rejection

All of the claims pending in the last response, claims 64 to 67, 71, 72, 76 to 78 and 80 to 113, were rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabling. Applicants respectfully traverse the rejection, noting that many of the claims under this rejection have been canceled herein without prejudice, while several new claims have been added herein.

1. The Examiner's position on what scope of the claims is enabling

As an initial matter, it is not completely clear to Applicants what the Examiner's position is on this crucial issue. Applicants fear that the Examiner's position is that the only claims he will allow are those directed to SEQ ID NO:10, and SEQ ID NO:10 only. This is despite the fact that Applicants have disclosed other sequences of heparanase protein with vastly different sequences than SEQ ID NO:10, as well as guidance for making further variants, as discussed below.

In this regard, Applicants note that, with no discussion whatsoever on this particular point, the Examiner has rejected, for example, claim 111, which does not recite any homology percentage at all. The Examiner has also rejected, for example, claim 109, which requires at least 90% homology with SEQ ID NO:10, as well as claim 110, which merely requires at least 95% homology to SEQ ID NO:10.

Is it the Examiner's position that only SEQ ID NO:10 itself is enabling, despite the disclosure of other heparanase proteins and despite the guidance (discussed at length below) of how the skilled artisan can modify such proteins and very likely retain activity?

Would it be meaningful protection to Applicants to have all claims limited to SEQ ID NO:10? What if an infringer was to merely add an amino acid residue to SEQ ID NO:10 (on either the C- or N-terminus)? Or what if an infringer was to take Applicants' **own** alignment guidance, as disclosed for example in Figure 17 of the specification, and make even a single substitution in a variable region of one similar amino acid for another (say, for example, one acidic and hydrophilic amino acid for another)? Indeed, the infringer could make substitutions in the variable regions by replacing an amino acid residue in SEQ ID NO:10 with the corresponding residue of mouse or rat heparanase, as taught in the subject application! In such instances of infringement, why should Applicants' be forced to hope to be protected by something as nebulous as the "doctrine of equivalents" when Applicants deserve so much more (i.e., the literal scope of the claims!), given the disclosure of the subject application?

At the very least, Applicants respectfully request that the Examiner reconsider and articulate a position on this issue that is fair and reasonable. Thus far, with all due respect, the Examiner's position on this issue can only be characterized as being extremely generous to potential infringers.

2. The Examiner's position on what enables a genus

The Examiner seems to take the position that the skilled artisan must be able to "make and use the vast majority of claimed polypeptides" for there to be enablement (Office Action, page 4). This position is simply not the law.

As stated in the MPEP (2164.08(b): "The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)."

As Applicants will show below, the human, mouse and rat polypeptide sequences disclosed, as well as the alignment information gleaned from these sequences, gives the skilled artisan ample guidance for "expenditure of no more effort than is normally required in the art."

If the Examiner still feels that his position on what is required to enable a genus is correct, Applicants invite him to cite even a few issued U.S. patents with genus chemical composition claims with any meaningful breadth where such a standard was met and, therefore, where the "vast majority" of species within the genus were actually enabled (by being made and tested and found to be active).

If the Examiner's position was correct, a claim to a polypeptide with virtually any percentage of homology would never be allowed, because the "vast majority" of species within the generic claims were not shown to be active.

If the Examiner's position was correct, a claim "comprising" a polypeptide (even with 100% homology) would never be allowed even if a million species within the claim's scope were exemplified because "comprising" makes species within the scope of the claim limitless and even ascertaining (let alone exemplifying) the "vast majority" of species within such a claim would be impossible.

Of course, this is not the law and it is not consistent with common practice at the USPTO. Rather, species can be likened to "poles" and the genus to a "tent." Several well placed species "poles" (for example, like Applicant's heparanase homologs, which span 65% homology!) can support the genus "tent." Having the "vast majority" of the space of the genus "tent" occupied by species "poles" is not necessary and out of touch with the reality of chemical genus practice and allowance.

3. The alignment data

Applicants now turn their attention to the alignment data, as shown for example in Figure 17 of the specification. The Examiner has argued that "the specification does not establish . . . regions of the protein structure which may be modified without effecting heparanase catalytic activity . . . a rational and predictable scheme for modifying any amino acid residue of a heparanase with an expectation of obtaining the

desired biological function." Applicants respectfully take issue with the Examiner's position.

As supported by the attached Declaration from one of the inventors of the subject invention, analysis of the alignment data shown in Figure 17 provides ample guidance to the skilled artisan on how to make active heparanase variants. For example, residues 85 to 106 are identical among the variants shown in Figure 17. By contrast, for example, residues 23 to 36 have 11 residue differences.

Similarly, comparing rat and human, residues 129 to 138, for example, have 8 differences among the 10 residues, with 9 of 10 differences among mouse and human at this region. With such guidance, the skilled artisan would know to not vary residues 85 to 106 and to vary one or more residues among residues 23 to 36 and/or 129 to 138, especially with a similar substitution (e.g., hydrophilic) as discussed above. The skilled artisan could even further use the guidance of the subject specification to replace one or more amino acid residues in SEQ ID NO:10, especially in these highly variable regions, with those corresponding residues found in mouse or rat heparanase. See Declaration, paragraph 2.

Indeed, looking at the protein more broadly, residues 49 to 109 make up 61 residues. Comparing mouse and human region at this region, there are only 10 of 61 changes. Comparing rat and human at this region, there are also only 10 of 61 changes. This is a remarkably conserved region, one that the skilled artisan would likely not vary, at least as a starting point, in trying to obtain additional heparanase homologs. Declaration, paragraph 3.

And, as it turns out, the conserved region of residues 49 to 109 was confirmed to be the 8 kDa unit of active heparanase. By contrast, variable regions 23 to 36 and 129 to 138, discussed above, are not part of either the small or large units of mature heparanase. Declaration, paragraph 3.

In summary, the specification discloses three variants of heparanase that span about 65% homology among them. More importantly, alignment of these variants, as shown in Figure 17 of the specification, and the wealth of information that can be

gleaned from analyzing such alignment, provides ample guidance for the skilled artisan to make even more variants.

Finally, to limit the subject claims to SEQ ID NO:10 would be grossly unfair. It would allow a potential infringer to easily skirt the claims based on the guidance provided by **the subject application**! Accordingly, withdrawal of this rejection is respectfully requested.

D. Regarding the anticipation rejection

All of the claims pending in the last response, claims 64 to 67, 71, 72, 76 to 78 and 80 to 113, were rejected under 35 U.S.C. § 102 as allegedly anticipated by Fuks et al. (U.S. Pat. No. 5,362,641; hereinafter "Fuks"). Applicants respectfully traverse the rejection, noting that many of the claims under this rejection have been canceled herein without prejudice, while several new claims have been added herein.

Applicants have four sets of claims pending and, therefore, make four distinctions of Fuks based on these claim sets.

1. Elicitation of anti-heparanase antibodies

Claims 97 to 101, as currently amended, are directed to a "preparation" that "can elicit anti-heparanase antibodies." By contrast, as stated in previous responses and declarations, including the one attached hereto, the preparation taught by Fuks could not elicit anti-heparanase antibodies. See Declaration, paragraph 6. Indeed, the previous Office Action (at page 8) acknowledges that the preparation of Fuks does not elicit anti-heparanase antibodies. Accordingly, Fuks does not anticipate claims 97 to 101.

For purposes of clarity, Applicants further note that claims 97 to 101 are not directed to a preparation with the "potential" to elicit anti-heparanase antibodies. For example, it has been argued in prior Actions that the preparation of Fuks has the "potential" to elicit anti-heparanase antibodies if further purified. That would be like saying that a preparation of albumin has the "potential" to elicit anti-heparanase antibodies if the albumin was replaced with heparanase.

In any event, claims 97 to 101 are not directed to what "potentially" can be done to a preparation to allow it to elicit anti-heparanase antibodies. Rather, claims 97 to 101 are directed to a preparation as is. The claimed preparation as is can elicit anti-heparanase antibodies. By contrast, the preparation taught by Fuks cannot. Accordingly, withdrawal of this rejection with respect to claims 97 to 101 is respectfully requested.

2. Close to homogeneity

Claims 107 to 110 are directed to heparanase that is purified "close to homogeneity." By contrast, the heparanase taught by Fuks is not purified "close to homogeneity."

As defined in a biology dictionary and as is commonly understood in the art, "homogeneity" means purity. See attached Exhibit A, page 222. Applicants have examined the heparanase of Fuks. No one skilled in the art would consider it to be "close to" homogeneity or purity. As disclosed in prior declarations, as well as in the attached, the heparanase of Fuks was inextricably mixed with a significant amount of at least six other proteins, PAI-1, Nexin-I, Vimentin, Grp94/endoplasmin, FLT receptor and Tryptase. See Declaration, paragraph 5. Indeed, the amount of these non-heparanase proteins present was so significant, that antibodies to one of these proteins (PAI-1) were elicited, while antibodies to heparanase were not. See Declaration, paragraph 6.

Under these facts, no one skilled in the art would consider the heparanase taught by Fuks to be remotely close to "homogeneity" or purity. Declaration, paragraph 7. Accordingly, withdrawal of this rejection with respect to claims 107 to 110 is respectfully requested.

3. Purified

Claims 114 to 118 are directed to "purified" heparanase. "Pure" is defined in a common biology dictionary, as well as commonly known in the art, as containing no contaminating material. See Exhibit A, page 393.

As discussed above, the heparanase of Fuks was far from "pure." It was inextricably mixed with significant amounts of contaminating material. So much so that

antibodies were elicited from the contaminating material, and antibodies could not be elicited from the heparanase of Fuks because it was so contaminated.

No one skilled in the art would consider the heparanase of Fuks to be "pure." See Declaration, paragraph 8. Accordingly, claims 114 to 188 are not anticipated by Fuks.

4. Isolated

Claims 71, 72 and 92 to 96 are directed to "isolated" heparanase. The term "isolate" is defined in a biology dictionary, and is commonly understood in the art, as to "separate and purify." See Exhibit A, page 255.

As discussed above, the heparanse of Fuks was far from "pure" and far from being "isolated" in any meaningful sense. Rather, it was inextricably mixed with significant amounts of contaminating material. So much so that antibodies were elicited from the contaminating material, and antibodies could not be elicited from the heparanase of Fuks because it was so contaminated.

No one skilled in the art would consider the heparanase of Fuks to be "isolated." See Declaration, paragraph 9. Accordingly, Applicants respectfully request that the rejection of claims 71, 72 and 92 to 96 as allegedly anticipated by Fuks be withdrawn.

III. CONCLUSION

All of the issues raised in the Office Action have been addressed and are believed to have been overcome. Accordingly, it is respectfully submitted that all the claims under examination in the subject application are allowable. Therefore Applicants respectfully request a Notice of Allowance to this effect.

Respectfully submitted,

Martin O Moynihan

Martin Moynihan,
Registration No. 40,338

Date: July 19, 2005

Encl.:
RCE
Request for Extension of Time
Declaration

IN THE INSIGHT UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PECKER et al

Serial No.: 09/776,874

Filed: February 6, 2001

Group Art Unit: 1652

For: Polynucleotide Encoding A Polypeptide Having Heparanase Activity and Expression of Same in Genetically Modified Cells

Attorney Docket: 01/21603

Examiner: R. G. Hutson

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION UNDER 37 U.S.C. SECTION 1.131

Sir:

I, Iris Pecker, declare as follows:

1) I am the Iris Pecker who is an inventor named in the above-identified subject invention.

2) I have analyzed the alignment data shown in Figure 17 of the subject application. In my opinion, it provides ample guidance to the skilled artisan on how to make active heparanase variants. For example, residues 85 to 106 of human heparananse (SEQ ID NO:10) are identical to the corresponding residues of the variants shown in Figure 17. By contrast, for example, residues 23 to 36 have 11 residue differences. Similarly, comparing rat and human heparanase, residues 129 to 138, for example, have 8 differences among the 10 residues, with 9 of 10 differences among mouse and human at this region. With such guidance, the skilled artisan would know to not vary residues 85 to 106 and to vary one or more residues among residues 23 to 36 and/or 129 to 138, especially with a similar amino acid residue substitution (e.g., hydrophilic). The skilled artisan could even further use the guidance of the subject specification to replace one or more amino acid residues in SEQ ID NO:10, especially in these highly variable regions, with those corresponding residues found in mouse or rat heparanase.

3) Looking at heparanase protein more broadly, residues 49 to 109 make up 61 residues. Comparing mouse and human region at this region, there are only 10 of 61 changes. Comparing rat and human at this region, there are also only 10 of 61 changes. This is therefore a very conserved region, one that the skilled artisan would likely not vary, at least as a starting point, in trying to obtain additional heparanase homologs.

4) The conserved region of residues 49 to 109 was confirmed to be the 8 kDa unit of active heparanase. By contrast, variable regions 23 to 36 and 129 to 138, discussed in paragraph 2 above, are not part of either the small or large units of mature heparanase.

5) I have also reviewed an analysis of the heparanase taught by Fuks et al. (U.S. Pat. No. 5,362,641; hereinafter "Fuks"). This analysis shows that the heparanase of Fuks was inextricably mixed with a significant amount of at least six other proteins: PAI-1, Nexin-I, Vimentin, Grp94/endoplasmin, FLT receptor and Tryptase.

6) Indeed, the amount of these non-heparanase proteins present was so significant, that antibodies to one of these proteins (PAI-1) were elicited, while antibodies to heparanase could not be.

7) Based on this analysis, in my opinion, the skilled art would not consider the heparanase taught by Fuks to be remotely close to homogeneity or purity.

8) Based on this analysis, in my opinion, the skilled art would not consider the heparanase taught by Fuks to be purified heparanase.

9) Based on this analysis, in my opinion, the skilled art would not consider the heparanase taught by Fuks to be isolated heparanase.

I declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willfully false statements are punishable by fine or imprisonment under 18 U.S.C. Section 1001 and that any such statement may jeopardize the validity of the subject application or any patent issued thereon.

Ir Pecker

Dr. Iris Pecker

14/7/05

Date

RCE & 2FW

PTO/SB/30 (08-00)
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REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Subsection (b) of 35 U.S.C. § 132, effective on May 29, 2000, provides for continued examination of an utility or plant application filed on or after June 8, 1995. See The American Inventors Protection Act of 1999 (AIPA).

Application Number	**09/776,874**
Filing Date	**1 March 1999**
Examiner Name	**R. G. Hutson**
First Named Inventor	**Iris PECKER**
Group Art Unit	**1652**
Attorney Docket Number	**01/21603**

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.

NOTE: 37 C.F.R. § 1.114 is effective on May 29, 2000. If the above-identified application was filed prior to May 29, 2000, applicant may wish to consider filing a continued prosecution application (CPA) under 37 C.F.R. § 1.53 (d) (PTO/SB/29) instead of a RCE to be eligible for the patent term adjustment provisions of the AIPA. See *Changes to Application Examination and Provisional Application Practice*, Final Rule, 65 *Fed. Reg.* 50092 (Aug. 16, 2000); Interim Rule, 65 *Fed. Reg.* 14865 (Mar. 20, 2000), 1233 *Off. Gaz. Pat. Office* 47 (Apr. 11, 2000), which established RCE practice.

1. **Submission required under 37 C.F.R. § 1.114**
   - a. ☐ Previously submitted
     - i. ☐ Consider the amendment(s)/reply under 37 C.F.R. § 1.116 previously filed on _____ (Any unentered amendment(s) referred to above will be entered).
     - ii. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
   - b. ☒ **Enclosed**
     - **i. ☒ Amendment/Reply**
     - ii. ☐ Affidavit(s)/Declaration(s)
     - iii. ☐ Information Disclosure Statement (IDS)
     - **iv. ☒ Other Three (3) Month Extension fee**
     - **v.** ☐ Other
2. **Miscellaneous**
   - a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. § 1.103(c) for a period of ____ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. § 1.17(i) required)
   - b. ☐ Other _____
3. **Fees** The RCE fee under 37 C.F.R. § 1.17(e) is required by 37 C.F.R. § 1.114 when the RCE is filed.

			SMALL ENTITY RATE	FEE	OTHER THAN A SMALL ENTITY RATE	FEE
Request for Continued Examination (RCE)			1	$ 395		$ 790
Multiple Dependent Claims			0 x $ 180	$ 0	x $ 360	$
Total Claims	22 - 20=	2	2 x $ 25	$ 50	x $50	$
Independent Claims*	4 - 3=	1	1 x $ 100	$ 100	x $200	$
			TOTAL	$545	*TOTAL*	$

☒ **The Commissioner is hereby authorized to charge $545.- filing fees to Deposit Account No. 50-1407. In the event additional fees are required, please charge these additional fees to Deposit Account No. 50-1407. In the event of overpayment, please credit Deposit Account No. 50-1407.**

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print/Type)	Martin Moynihan	*Registration No. (Attorney/Agent*	40,338
Signature	Martin O Moynihan	*Date*	**July 19, 2005**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	§	
Iris PECKER, et al.	§	
Serial No.: 09/776,874	§	
Filed: February 6, 2001	§	Group Art Unit: 1652
For: Polynucleotide Encoding A Polypeptide Having Heparanase Activity and Expression of Same in Genetically Modified Cells	§	
	§	Attorney Docket: **01/21603**
Examiner: R. G. Hutson	§	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION AND FEE FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Sir:

(1) This is a petition for an extension of time to respond to the Final Office Action mailed January 26, 2005, for a period of three (3) months.

(2) Applicant is a:
_X_ small entity ___ verified statement attached
___ verified statement filed

3. Extensions (months)	Fees for small entity	Fee for other than small entity
☐ one month	$ 60.00	$ 120.00
☐ two months	$ 225.00	$ 450.00
☑ three months	**$ 510.00**	$ 1020.00
☐ four months	$ 795.00	$ 1590.00
☐ five months	$1080.00	$ 2160.00

(4) An amendment _X_ is filed herewith
___ has been filed

(5) Please charge the extension fee and any other amount required to Deposit Account No. **50-1407**. A duplicate copy of this form is enclosed.

Respectfully submitted,

Martin O. Moynihan

Martin Moynihan
Registration No. 40,338

July 19, 2005